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REVIEW

External adjuncts to enhance fracture healing: What is the role of ultrasound?

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Summary Current methods of fracture care use various adjuncts aimed at decreasing time to fracture union and improving fracture union rates. Among the most commonly used modalities, low-intensity pulsed ultrasound is emerging as a safe, cost-effective and reliable treatment for both fresh fractures and fracture nonunions. Both in vivo and in vitro basic science studies have helped to elucidate potential mechanisms of ultrasound action and a number of prospective, randomised, double-blind, placebo-controlled trials exist demonstrating the clinical efficacy of low-intensity pulsed ultrasound. This article will review the evidence for the use of low-intensity pulsed ultrasound in fracture care.

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Introduction

While advances in the operative and non-operative care of fractures continue to improve patient outcomes, under the best of circumstances, recovery times are often on the order of months. This can have profound personal and economic consequences for patients and their families, underscoring the tremendous cost to the health care system. When fractures fail to heal, costs become even greater. Five to 10% of the 5.6 million fractures that occur annually in the US are complicated by delayed healing or nonunion.[3] As an example, the tibia is the most commonly fractured long bone and accounts for 35–65% of all nonunions. This has a substantial economic impact when one considers re-operations, secondary surgical procedures, and prolonged physical therapy in treating these fractures.[16] The need to decrease healthcare spending has led to interest in modalities which can enhance and hasten healing of fractures, diminish the incidence of nonunions, and in the event of delayed or nonunion treat them effectively.

Many modalities have been used in an attempt to accelerate fracture healing and prevent delayed and/or nonunions. These include autogenous and allogenic bone grafting, alteration of the mechanical stiffness of the fixation devices, electromagnetic fields, high-frequency low-magnitude mechanical stimuli, and ultrasound. Disadvantages of bone grafting and implantation of electrical stimulators are that these procedures must be performed in the operating room and often require a hospital admission. The result is added morbidity to the patient and added cost to the health care system.

Ultrasound has many medical applications, including diagnostic, operative, and therapeutic usages.[15] Extracorporeal shock wave therapy (orthotripsy) has been used in the treatment of nonunions, with the premise that these high-energy waves cause microfracture of the trabeculae and through this tissue damage, encourage the reparative process to resume, leading to fracture union.[35,39,43] In fact, prospective, non-randomised studies report more than 700 patients with documented healing success rates of 62–83%.[28] The appeal of this treatment option is that it performed externally. However, the practicality of shock wave therapy is questionable because it is painful and its use requires anaesthesia and often a hospital admission following treatment.[35,39,43]

As a result of continuing investigation into superior methods of external stimulation of fracture healing, low-intensity pulsed ultrasound has emerged as a safe and effective modality to enhance fracture healing. As with shock wave treatment, low-intensity pulsed ultrasound is applied externally, however, it is painless and can be applied by the patient on a daily basis from the patient's home. In October 1994, the United States Food and Drug Administration approved the use of ultrasound in fresh fractures and subsequently approved its use for established nonunions in February 2000.[36] A number of prospective, randomised, double-blind, placebo-controlled trials have demonstrated the efficacy of ultrasound in accelerating fracture healing. This is likely due to the influence of ultrasound at each key stage of fracture healing, including inflammation, repair, and remodeling. Moreover, ultrasound has been shown to affect angiogenesis, chondrogenesis, and osteogenesis.[36] The purpose of this review is to describe how ultrasound enhances fracture healing at a cellular and molecular level, describe in vitro and animal studies, and then to review relevant clinical fracture and nonunion studies.

Pathophysiological principals

Overview of fracture healing

Fracture healing is a form of wound repair and is driven by the recruitment of cells and the expression of genes. It is generally divided into three stages: inflammatory, reparative, and remodeling. The inflammatory stage commences with the disruption of blood vessels from the injury and the formation of a haematoma. Inflammatory cells invade the haematoma and initiate lysosomal degradation of necrotic tissue.[13]

The reparative phase begins within 4–5 days following the fracture. Pluripotential mesenchymal stem cells invade the area and differentiate into fibroblasts, chondroblasts, and osteoblasts. These cells are responsible for the formation of a soft fracture callus and the subsequent formation of woven bone. Angiogenesis within the marrow cavity and the periosteal tissues helps to deliver the appropriate cells to the fracture site. Cartilage cells are present in the fracture site as early as 5 days post-injury, and the soft callus is formed, stabilising the fractured ends of the bone. The process of osteoid formation, mineralisation, and creation of woven bone thus commences.[13]

The final step in the process of fracture healing is the remodeling stage, which can continue up to several years following the fracture. Fracture callus is remodelled from immature woven bone into mature lamellar bone. The end result is mature lamellar bone oriented along lines of stress creating normal or near-normal morphology and strength without a trace of scar.[13]

The definition of a delayed union is generally accepted to be healing not completed by 3 months. Of these delayed unions, some will still remain ununited at 9 months post-fracture and are thus classified as nonunions.[13] Many factors, both local and systemic, have been associated with delayed fracture healing (see Table 1).[8,13,15]

Table 1 Factors implicated in delayed fracture healing

Local factors	Systemic factors
Blood supply to the bone	Patient age
Fracture location	Gender
Fracture type	Hormonal effects
Bone loss	Smoking
Open fracture	Diabetes
Post-operative infection	Alcoholism
Extent of soft tissue damage	
Fracture gap and soft tissue interposition	
Pre-reduction displacement	
Poor stabilisation or fixation	

Mechanism of ultrasound action: in vitro and in vivo evidence in fracture healing

Mechanical signal transduction

Modalities such as adding mechanical stimuli, electromagnetic fields, and ultrasound serve to take the place of the normal functional loading that would occur under physiological conditions and represent one pathway by which ultrasound may exert it effect on fracture healing (Table 2).[8,13] Cells in bone are equipped with mechanisms to sense diverse physical forces to transduce signals for adjustment of their microenvironment and modalities such as ultrasound produce these mechanical stimuli.[26] Ultrasound transmits energy to tissues as high-frequency pressure waves and as a surgical instrument requires energy levels of 5–300 W/cm^2 to fragment caculi, ablate cataracts, or remove methylmethacrylate in revision hip arthroplasty. High-intensity (1.0 W/cm^2) continuous-wave ultrasound was deleterious to fracture healing in animal studies, while low-intensity (30 mW/cm^2) pulsed ultrasound signal can accelerate fracture healing.[13,22,32,42,44]

As ultrasound waves pass through tissues, absorption of the waves is proportionate to the density of the tissue. This may explain how ultrasound therapy can be targeted to the fracture gap, since bone is of increased density than the surrounding soft tissues.[13] In addition, in areas such as the bone–muscle and bone–callus interfaces, much of the incident radiation energy is reflected, creating pressure variations throughout the tissue.[18] Therefore, the cells themselves may sense this mechanical alteration in their environment and must then translate this change into a molecular response, thus modulating cell function.[13]

Table 2 Potential mechanisms of low-intensity pulsed ultrasound (LIPUS) effect on fracture healing

Mechanical signal transduction and induction of gene expression
Activation of enzymes in response to heat energy
Increased vascularity at the fracture site
Modulation of intracellular calcium signalling
Enhanced cartilage calcification and maturation

Table 3 Genes expressed in response to low-intensity pulsed ultrasound (LIPUS)

Gene	Function
Aggrecan	Constituent of cartilage
Osteopontin and osteocalcin	Non-collagenous proteins found in bone
Major histocompatibility Class I antigen	Immunologic pathways
Cyr61	Growth factor involved in chondrogenesis
Phosphoglucomutase	Glycolytic enzyme
c-fos	Immediate early gene
Insulin growth factor-1 (IGF-1)	Anabolic gene

Evidence of this molecular response is that a number of genes are expressed in response to low-intensity pulsed ultrasound and these gene products seem to play a key role in callus formation and stability[13,26,46,47] (Table 3). For instance, cultured chondrocytes up-regulate expression of the aggrecan gene when exposed to low-intensity pulsed ultrasound and a similar up-regulation of aggrecan gene expression was shown in rat femur fractures.[46,47] The increased aggrecan gene expression was correlated with an increase in torsional strength of the calluses treated with ultrasound.[47] Others have found an up-regulation of anabolic genes in osteoblasts from rat femora.[26]

In addition to gene activation and expression, low-intensity pulsed ultrasound may modify the activity of gene products in the fractures site. For example, absorption of ultrasound waves converts this mechanical energy to heat, and it is known that some enzymes, such as collagenase, are sensitive to even slight variations in temperature.[45]

Ultrasound effect on vascularity at the fracture site

Blood supply is a central concern for tissue healing and it is widely recognised that medical co-morbidities leading to decreased blood flow will decrease the ability to heal fractures. It has been shown in a dog ulna model that low-intensity pulsed ultrasound treatment for 10 days increases the degree of vascularity, implying that ultrasound increases blood flow to the healing fracture site.[31] Others have shown that low-intensity pulsed ultrasound leads to stimulation of vascular endothelial growth factor (VEGF) during fracture healing.[21]

The role of calcium

There is evidence to suggest that ultrasound stimulates osteogenesis through calcium signaling and calcification of cartilage. Low-intensity pulsed ultrasound has been shown to increase the levels of intracellular calcium incorporation in cultures of differentiating bone and cartilage cells. Concurrently, TGF-beta and adenylate cyclase activity were modulated with these increases in calcium incorporation.[37,38] In addition, low-intensity pulsed ultrasound can increase the intracellular calcium concentration in chondrocytes and increase the percentage of calcified cartilage in the physis in fetal mice. These results suggest a stimulatory effect of low-intensity pulsed ultrasound on endochondral ossification is due to stimulation of bone cell differentiation and calcified matrix production.[19,29]

Timing of ultrasound effects

Another question to be answered is at which stage in the fracture repair process does ultrasound exert its effects? Azuma et al.[1] investigated this question using a rat femoral fracture model which used intramedullary fixation with a Kirschner wire. Fractures were exposed to low-intensity pulsed ultrasound at different periods following fracture: days 1—8; days 9—16; days 17—24; and throughout, from days 1 to 24. Animals were sacrificed on day 25 and measurements of hard callus area, bone mineral content, mechanical torsion properties were made, along with histologic analysis. The authors found that the low-intensity ultrasound-treated femurs showed statistically significant increases in mechanical properties (maximal torque and stiffness) and more advanced endochondral ossification in all groups when compared with the control group. The authors conclude that their results suggest that low-intensity pulsed ultrasound acts on some cellular reactions at each stage of the facture healing process. Similar improvements in torsional and histologic properties of rat femoral fractures treated with ultrasound have been found by Wang et al.[44]

Acceleration of bone formation in addition to fracture healing

The use of ultrasound in arthrodesis

In addition to animal models of long bone healing, there is evidence of improved spinal arthrodesis rates with the use of ultrasound. Glazer et al.[12] compared arthrodesis rates in New Zealand white rabbits undergoing spinal fusion with autologous bone with the addition of ultrasound to a group that received autologous bone grafting, only. There was a statistically significant decrease in the pseudoarthrosis rate from 35% in the control group to 7% in the group that received ultrasound treatment. Biomechanical testing showed a superior fusion mass in those animals treated with ultrasound, as there was a significant increase in stiffness (33%; $p = 0.03$) and load to failure (24%; $p = 0.04$). Analysis of histology slides from the fusion mass showed a qualitative increase in bone formation. In a later study using a canine fusion model, Cook et al.[5] showed a 100% fusion rate in animals treated with ultrasound, while the control group had a 78% radiographic fusion rate and a 44% histological fusion rate. Additionally, there was an increase in mechanical stiffness in the ultrasound-treated fusion sites. These differences were statistically significant.

Distraction osteogenesis

Use of ultrasound has also been applied to a distraction osteogenesis model in rabbits.[40] Callotasis of the tibia was performed on Japanese white rabbits using mini-external fixators. In animals undergoing "normal distraction", a waiting period of 7 days was followed by a distraction period of 10 days with a distraction rate of 0.5 mm/12 h. Other animals underwent "fast distraction" with a waiting period of 0 days and a distraction rate of 1.5 mm/12 h to simulate sub-optimal conditions for osteogenesis. In each of these groups a selected number of tibias were treated with low-intensity ultrasound (30 mW/cm^2) for 20 min daily after ceasing distraction. In those tibias undergoing normal distraction, the authors found a significant increase in the percentage of hard callus in the area of the fracture gap at days 7 and 14 in the ultrasound group, as well as a significant increase in bone mineral density at these time points in the ultrasound group. Mechanical testing showed the ultrasound group to be ahead of the control group by 1 week, although these values did not reach statistical significance. When ultrasound was used in tibias undergoing fast distraction, there was a statistically significant increase in percentage of hard callus. The authors suggested that treatment with ultrasound was effective in achieving bone maturation, even under adverse conditions, and correlated this to clinical evidence of accelerated healing in smokers[4] with smoking as a cause of a poor environment for bone healing. Similar results of significantly increased maturation of regenerate bone were shown in a sheep model by Mayr et al.[24]

Clinical evidence

The use of ultrasound as an external adjunct in fresh fractures

Beyond the laboratory and animal studies, clinical research suggests a therapeutic benefit of low-intensity pulsed ultrasound in the treatment of fresh fractures as well as delayed unions and nonunions. Duarte reported an 85% success rate in a 12-year review of the use of low-intensity pulsed ultrasound for 385 delayed and nonunions with a mean fracture age of 14 months.[7,13] These results are similar to reported results of Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc., Piscataway, NJ). They report a 91% healing rate in 1700 delayed unions and an 85% healing rate in 700 nonunions with a mean fracture age of 24 months.[13] Improving upon the above retrospective data, a number of prospective, randomised, double-blind, placebo-controlled trials offer a higher level of evidence for the efficacy of ultrasound (Table 4).

Ultrasound use in tibia fractures treated non-operatively

Heckman et al.[15] performed a multi-institutional study to examine the efficacy of ultrasound usage for tibial shaft fractures. Included were closed and Grade I open diaphyseal fractures and that were treated non-operatively with closed reduction and casting. There were 67 patients in this group. Thirty-three patients with a mean age of 36, were in the experimental group (76% men), while 34 patients with a mean age of 31 were in the control group (85% men). There were two Grade I open fractures in the experimental group and one in the placebo group. Patients were given either the ultrasound device (consisting of a burst width of 200 μs containing 1.5 MHz sine waves, with a repetition rate of 1 kHz, and a pressure wave applied at the fracture site of 30 mW/cm^2) or a placebo device. Ultrasound treatment was begun through a window in the cast within 7 days of fracture and consisted of a 20 min period each day. Treatment was continued for 20 weeks or until the fracture was sufficiently healed and healing was determined by clinical examination and by radiographic evidence of three of four cortices healed. Investigators were blinded as to ultrasound or control groups when evaluating radiographs for evidence of healing.

Favourable results were shown with ultrasound treatment. There was a statistically significant decrease in time to clinical healing, with a mean of 86 days in the ultrasound group compared with 114 days in the control group ($p = 0.01$). Moreover,

Table 4 Summary of prospective, randomised, double-blind, placebo-controlled clinical studies using low-intensity pulsed ultrasound (LIPUS)

Study	Fracture type	Number of patients	Outcome	Statistical significance, p
Heckman et al.	Tibial shaft	67	Decreased time to union; 96 days with LIPUS vs. 154 days in control group	0.0001
Kristiansen et al.	Distal radius	60 (61 fractures)	Decreased time to union; 61 days with LIPUS vs. 98 days in control group	<0.0001
Mayr et al.	Scaphoid	30	Decreased time to union; 43 days with LIPUS vs. 62 days in control group	<0.01
Cook et al.	Tibial shaft and distal radius in smokers	111	Decreased time to union of tibial shaft fractures in smokers by 41%; 103 days with LIPUS vs. 175 days in control group	<0.006
			Decreased time to union of distal radius fractures in smokers by 51%; 48 days with LIPUS vs. 90 days in control group	<0.003
Leung et al.	Open tibial shaft	30	Decreased time to appearance of first bridging callous; 6.5 weeks with LIPUS vs. 9.5 weeks in control group	<0.05
			Increased bone mineral content and plasma bone-specific alkaline phosphatase	<0.05
Emami et al.	Tibial shaft with intramedullary nail	32	No difference in fracture healing time; 113 days with LIPUS vs. 112 days in control group	No statistical significance
Emami et al.	Tibial shaft with intramedullary nail	30	No difference in serum levels of alkaline phosphatase or osteocalcin	No statistical significance

All studies used the Sonic Accelerated Fracture Healing System (SAFHS 2A) (Exogen, Inc., Piscataway, NJ). Patients were treated with an ultrasound signal with a burst width of 200 μs (±10%) containing 1.5 MHz (±5%) sine waves, with a repetition rate of 1 kHz (±10%) and a spatial average temporal intensity of 30 mW/cm^2 (±30%).

they found a significant decrease in time to overall healing, both clinical and radiographic, with 96 days in the ultrasound group compared with 154 days in the control group ($p = 0.0001$). There were no serious complications from ultrasound use and patient compliance with the ultrasound device was excellent.

Ultrasound use in acute distal radius fractures treated non-operatively

Kristiansen et al.[20] reported a multi-centre clinical trial which showed the efficacy of ultrasound in accelerating healing of distal radial fractures. They included men and non-pregnant women of at least 20 years of age who had closed, dorsally angulated, metaphyseal fractures of the distal radius within 4 cm of the tip of the radial styloid, including those fractures with intra-articular extension and associate ulnar styloid fracture, sustained within 7 days of presentation. Fractures included in this study also met the criteria of being satisfactorily reduced and immobilised in a short arm cast. There was a total of 61 fractures (in 60 patients) included in the final analysis, with 30 fractures in the ultrasound group and 31 fractures in the placebo group. There was no difference in co-morbidities between these groups. The placebo group consisted of a device identical to the ultrasound device, except that it did not emit ultrasound energy (a "dummy machine"). Patients were followed at regular intervals with clinical and radiographic examination, and time to healed fractures was defined as clinical healing without pain or instability at the fracture site and radiographic evidence of bridging of the dorsal, volar, radial, and ulnar cortices.

There was a significant difference in time to union with the use of ultrasound, with the ultrasound group healing in 61 ± 3 days compared with the placebo group in 98 ± 5 days ($p < 0.0001$). Log-rank life-table analysis clearly demonstrated accelerated healing. Specifically, at 42 days after the fracture, 6 (20%) of 30 fractures treated the active device healed compared with 1 (3%) of 31 fractures treated with the placebo device ($p < 0.05$). At 56 days, 15 (50%) of 30 fractures in the ultrasound group healed compared with 4 (13%) of the 31 fractures in the placebo group ($p < 0.002$). At 70 days, 21 (70%) of fractures in the active group healed compared with 6 (19%) in the control group ($p < 0.0001$). At 84 days post-injury, 27 (90%) of fractures in the ultrasound group healed compared with 10 (32%) in the placebo group ($p < 0.0001$). The time to trabecular healing and cortical bridging of fractures was also significantly shortened in the ultrasound-treated group.

For the subset of 15 ultrasound-treated and 17 placebo-treated fractures with greater than 10° of angulation prior to reduction, treatment with ultrasound was associated with a significant decrease in loss of reduction ($20 \pm 6\%$ compared with $43 \pm 8\%$; $p < 0.01$) as well as a significant decrease in the mean time until the loss of reduction ceased (12 ± 4 days compared with 25 ± 4 days; $p < 0.04$). This was probably related to acceleration of the early healing process, as evidenced by the time to bridging of the first cortex. Finally, use of the ultrasound device significantly reduced time to fracture healing in smokers (mean, 48 ± 5 days for patients treated with ultrasound compared with 98 ± 30 days in the placebo group; $p < 0.003$). Again, there were no adverse reactions or complications attributable to the ultrasound device.

Ultrasound use in acute scaphoid fractures treated non-operatively

Results similar to those of Heckman et al.[15] and Kristiansen et al.[20] were shown by Mayr et al.[25] in healing of fresh scaphoid fractures. In their study of 30 patients, they compared one group of patients with fresh scaphoid fractures treated with casting, only, and a second group treated with casting and low-intensity ultrasound daily for 20 min. Healing was assessed every 2 weeks by CT scans to measure areas of cancellous bone bridging in correlation to the diameter of the scaphoid. Fractures treated with ultrasound healed in 43.2 ± 10.9 days compared with 62 ± 19.2 days in the control group ($P < 0.01$). At 6 weeks after injury, trabecular bone bridging showed $81.2 \pm 10.4\%$ healed in the ultrasound group compared with $54.6 \pm 29\%$ in the control group ($p < 0.05$).

The efficacy of ultrasound in smokers

Cook et al.[4] explored the use of ultrasound in patients who smoke and found results similar to Kristiansen et al.[20] In their analysis, they combined the data from the tibial fracture cohort from Heckman et al.[15] with a second cohort of patients with distal radial fractures. The distal radial group consisted of acute closed fractures of the within 4 cm of the tip of the radial styloid which were primarily transverse with dorsal angulation (intra-articular fractures were included). These fractures were treated with closed reduction and casting, with 61 total patients. Thirty patients with a mean age of 54 years were in the experimental group (80% women) and 31 patients were in the control group.

Analysis of the 111 patients included in this study demonstrated significant differences between the ultrasound and placebo groups in both smokers and nonsmokers. Specifically, healing time in tibial fractures was reduced by 41% (from 175 days for he placebo device to 103 days with the ultrasound device) amongst smokers ($p < 0.006$) and by 26% (from 129 days in the placebo group to 96 with the ultrasound device) amongst nonsmokers ($p < 0.05$). Healing time for distal radial fractures was reduced by 51% (from 98 to 48 days) in smokers ($p < 0.003$) and by 34% (from 100 to 66 days) amongst nonsmokers ($p < 0.0001$).

The use of ultrasound in acute tibia fractures treated with intramedullary fixation

Two prospective trials found no benefit in the use of low-intensity ultrasound in tibial shaft fractures following intramedullary fixation.[9,10] In the first trial,[9] serum levels of bone markers were measured prospectively for 1 year in 30 adult patients with an intramedullary fixed tibial fracture. Half of these patients received ultrasound. All fractures healed and there was no significant difference in healing between those treated with ultrasound (median, 113 days) and those in the placebo group (median, 112 days). Serum level of alkaline phosphatase and osteocalcin, both markers of bone formation, peaked at 10—16 weeks and showed no differences between patients who received ultrasound and those who did not. Interestingly, the marker for bone resorption, crosslinked telopeptide, peaked at 1—4 weeks and was lower in patients treated with ultrasound, suggesting that ultrasound might slow bone resorption.

In the second trial,[10] 15 patients were in the ultrasound group and 17 were in the placebo group. All patients were aged 16 of years or older and were treated for a closed or Grade I open primarily diaphyseal tibial fracture. Exclusion criteria included severe comminution or open physes, a Gustilo-type Grade II or III open fracture, multiple fractures, or other injuries, alcoholism or drug abuse, neuropathy, arthritis, malignant disease, steroid use, anticoagulant therapy, and use of bisphosphonates or non-steroidal anti-inflammatory drugs. There were 28 closed and 4 open fractures (3 in the ultrasound and 1 in the placebo group). The mean nail diameter was 11.5 mm and the nail was usually 0.5—1.0 mm smaller than the final reamer. Twenty-eight patients were allowed to be weight-bearing as tolerated and four were recommended to be partial weight-bearing following nail insertion. There was one smoker in each group. Use of low-intensity pulsed ultrasound was begun within 3 days of surgery and consisted of one 20-min treatment per day and lasted for 75 days.

Two time points were evaluated. The first was the time from fracture until evidence of callus formation and the second was healing time from initial fracture until three out of four cortices were bridged. The authors found no significant acceleration in fracture healing with the use of ultrasound. Time until first visible callus averaged 40 ± 3 days in the active treatment group and 37 ± 3 days for the placebo ($p = 0.44$). Healing time (bridging of three out of four cortices) was on average 155 ± 22 days for the active treatment group (median, 113 days) compared with 125 ± 11 days (median, 112 days) for the placebo group. One explanation could be that the metal implant inside the bone interferes with the effect of low-intensity ultrasound, since ultrasound probably works by creating low-level mechanical forces at the fracture site and intramedullary nailing might create a construct that it too stable for ultrasound to exert its effect. This is in contrast to Heckman's study[15] of tibias which did not have metal at the fracture site.

Use of ultrasound in high energy and open tibial fractures

A more recent prospective, randomised, double-blind, placebo-controlled trial was performed by Leung et al.[21] in patients with open tibial fractures and high-energy complex fractures, including comminuted and segmental fractures. All Gustilo Grade I and II shaft fractures were treated with locked intramedullary nails, while external fixators were used for Grade IIIa fractures. Sixteen patients were randomly selected to be in the treatment group and 14 were in the control group which used a "dummy machine". Ultrasound was used for 20 min per day for 90 days. The authors showed a significant decreased time to disappearance of tenderness at the fracture site (6.1 weeks versus 7.9 weeks; $p < 0.05$), earlier time to full weight-bearing in the treatment group (9.3 weeks compared with 15.5 weeks; $p < 0.05$); earlier time to removal of the external fixator in the treatment group (9.9 weeks compared with 17.1 weeks; $p < 0.05$); earlier appearance of the first bridging callus (6.5 weeks compared with 9.5 weeks; $p < 0.05$); as well as a statistically higher rate of bone mineral content acquisition and plasma bone-specific alkaline phosphatase in the treatment group. (Bone mineral content has been shown to correlate with mechanical stability of healing bones and bone-specific alkaline phosphatase is a biochemical marker of osteoblastic activity.) There was one delayed union in each group treated successfully with functional bracing and an additional 2 months of ultrasound. Four patients in the treatment group complained of mild erythema and swelling at the treatment site, although the symptoms disappeared after reassurance and the ultrasound treatment was not interrupted. This study suggests that fractures sustained from high-energy trauma with severe soft tissue injury and compromised blood supply can benefit from treatment with low-intensity pulsed ultrasound.

Meta-analysis of low-intensity pulsed ultrasound in acute fracture healing

Busse et al.[3] performed a meta-analysis of these randomised controlled trials of low-intensity pulsed ultrasound therapy for healing of fractures. Inclusion criteria included random allocation of treatments, inclusion of skeletally mature patients of either sex with one or more fractures, blinding of both the patient and the assessor(s) as to fracture healing, administration of low-intensity pulsed ultrasound treatments to at least 1 of the treatment groups, and assessment of fracture healing, as determined radiographically. Thorough review of the literature yielded six studies which fit these strict criteria (the study by Leung et al.[21] was more recent than this meta-analysis). Three, however, were excluded, as one was a repeat analysis of previously presented data and the others were of patients who were treated with an intramedullary nail prior to use of ultrasound.[4,9,10] Thus, three studies were included in the final meta-analysis.[15,20,25] Time to fracture healing was defined as bridging of at least three or four cortices and this information was extracted from the studies.

The treatment groups in all studies received daily 20-min sessions with an ultrasound signal composed of a burst width of 200 μs (±10%) containing 1.5 MHz (±5%) sine waves, with a repetition rate of 1 kHz (±10%) and a spatial average temporal intensity of 30 mW/cm^2 (±30%). Each group used the Sonic Accelerated Fracture Healing System (SAFHS 2A) (Exogen, Inc.). This pooled data of 158 fractures showed a mean difference in healing time of 64 days between the treatment and control groups, demonstrating the ability of ultrasound to provide a meaningful clinical benefit.

Ultrasound in the treatment of nonunion

In addition to acute fractures, low-intensity pulsed ultrasound has shown efficacy in treatment of established nonunions.[7] Gebauer et al.[11] prospectively entered patients with established nonunions into a trial of low-intensity pulsed ultrasound. Inclusion criteria were an established nonunion with a fracture age of at least 8 months, radiographic assessments showing the fracture healing process had not progressed for at least 3 months, and a minimum of 4 months without surgical intervention to remove any bias that might be introduced by a surgical procedure. Sixty-seven cases met these criteria and had a mean fracture age of 39 ± 6.2 months. Daily treatment with low-intensity pulsed ultrasound for 20 min per day for an average of 168 days yielded clinical and radiographic healing in 85% of cases (57 of 67). These results were statistically significant ($p < 0.00001$). Of the 10 non-healing fractures, 4 were scaphoid nonunions (mean fracture age of over 10 years). Smokers and past smokers tended to have lower healing rates, although these results did not achieve statistical significance. These results are similar to those previously reported, as Nolte et al.[27] reported healing in 25 of 29 nonunions (86%) and Mayr et al.[23] reported healing in 314 of 366 nonunions (86%) and 862 of 951 delayed unions (91%).

Ultrasound as an adjunctive therapy has been used in diverse clinical settings besides those listed above. Strauss and Gonya[41] reported two cases of failed arthrodeses in patients with charcot neuroarthropathy treated with revision surgery and adjuctive ultrasound to achieve stable unions. Additionally, ultrasound has been used successfully in a handful of patients with septic pseudoarthroses.[34] Others have reported successful use of ultrasound in the treatment of stress fractures of the tibia.[2,17]

The potential economic impact of ultrasound use in acute fractures

Heckman and Sarasohn-Kahn[16] hypothesised that it costs less money to pro-actively and adjunctively treat a population of tibial fractures with low-intensity pulsed ultrasound therapy when compared to patients treated by standard methods, alone. Reviewing the literature regarding the natural history of tibial fractures and time to union,[6,14,30,33] including their previously published work on acceleration of tibial fracture healing using low-intensity ultrasound,[15] they developed three economic models to characterise potential cost savings using this adjunctive therapy. All three models contained patients treated either conservatively or with an intramedullary nail. The first model does not use low-intensity pulsed ultrasound for either group. The second model uses low-intensity pulsed ultrasound for the conservatively treated group, only. In the third model, both the non-operative and the operative groups are given adjunctive low-intensity pulsed ultrasound. When the conservative (non-operative) treatment paths of model 1 and model 2 are compared, a cost savings of over $15,000 per case (40%) is realised as secondary procedures and Workers' Compensation costs are lowered when pulsed low-intensity ultrasound is added as an adjunct. Moreover, when the operatively treated groups in model 1 (no ultrasound) and model 3 are compared, a cost savings of over $13,000 per case is realised.

Conclusion

Amongst the modalities available to enhance fracture healing, ultrasound has emerged as a safe, practical, and effective treatment. As an adjunct to the care of fresh fractures, healing can be accelerated in a meaningful way, in the order of 40% in some instances.[3] Moreover, in the care of established fracture nonunions, ultrasound has likewise demonstrated its clinical efficacy. Low-intensity pulsed ultrasound is administered without pain, by the patient, at home, without the need for hospital admission, anaesthesia, or additional surgical procedures. Further studies will help to determine the role of ultrasound in fractures treated operatively, in particular, those tibial shaft fractures treated by intramedullary fixation. As economic costs of both fresh fractures and nonunions continue to burden our healthcare system, ultrasound therapy may play a significant role in the future of fracture care.

Conflict of interest

None of the authors has a financial relationship with Exogen or received any financial contribution.

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